IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

EXELIXIS, INC., Plaintiff, v. MSN LABORATORIES PRIVATE LIMITED and MSN PHARMACEUTICALS, INC., Defendants.	)	C.A. No. 22-228 (RGA) **CONSOLIDATED**

EXELIXIS' ANSWERING PROPOSED FINDINGS OF FACT
ON THE VALIDITY OF THE ASSERTED PATENTS

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TABLE OF ABBREVIATIONS

Abbreviation	Description
'439 patent	U.S. Patent No. 11,091,439 (JTX-1)
'440 patent	U.S. Patent No. 11,091,440 (JTX-2)
'015 patent	U.S. Patent No. 11,098,015 (JTX-3)
'349 patent	U.S. Patent No. 11,298,349 (JTX-4)
'473 patent	U.S. Patent No. 7,579,473 (DTX-13)
'776 patent	U.S. Patent No. 8,877,776 (JTX-9)
'549 patent	U.S. Patent No. 9,809,549 (JTX-10)
1-1 impurity	6,7-dimethoxy-quinoline-4-ol
ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
Asserted Claims	For the '349 patent, claim 3 For the '439 patent, claim 4 For the '440 patent, claim 3 For the '015 patent, claim 2
Exelixis	Exelixis, Inc.
FDA	United States Food and Drug Administration
FOF	Exelixis' Proposed Findings of Fact on MSN's Infringement
GRAS	Generally Recognized As Safe
GRASTAR	Granulated corn starch
MSN	MSN Laboratories Private Limited and MSN Pharmaceuticals, Inc.
MSN's ANDA	MSN ANDA No. 213878
MSN Op. Br.	MSN's Opening Brief, D.I. 169
MSN's Tablets	Proposed 20 mg, 40 mg, and 60 mg generic cabozantinib tablets that are the subject of MSN's ANDA

NDA	New Drug Application
Patents-in-Suit	’439 patent, ’440 patent, ’015 patent, and ’349 patent
POSA	Person of ordinary skill in the art
RFOF	Exelixis’ Rebuttal Proposed Findings of Fact on MSN’s Validity
Tr.	Final Trial Transcripts
UF	Uncontested Facts (D.I. 154, Ex. 1)
Zydus	Zydus Worldwide DMCC

TABLE OF WITNESSES

Witness	Live or By Deposition	Description
JoAnn Wilson, Ph.D.	Deposition	Former Vice President of Chemistry Manufacturing and Control at Exelixis and named inventor of the '349 patent. Tr. 564:7-10; Tr. 564:20-22; JTX-4 at 1.
Peter Lamb, Ph.D.	Deposition	Former Exelixis Chief Scientific Officer and named inventor of the Crystalline Malate Salt Patents. Tr. 577:1-6; JTX-1 at 1.
Khalid Shah, Ph.D.	Live	Dr. Shah is Senior Vice President of Pharmaceutical Operations, Manufacturing, and Supply Chain at Exelixis, and named inventor of the '349 patent. Tr. 586:17-21, 608:13-16 (Shah); JTX-4 at 1.
David MacMillan, Ph.D.	Live	Exelixis proffered and the Court accepted Dr. MacMillan as an expert in chemistry. Dr. MacMillan is a Nobel Prize-winning Professor of Chemistry at Princeton. Tr. 652:9-10, 653:12-16; Tr. 653:23-654:6 (MacMillan); PTX-776.
Allan Myerson, Ph.D.	Live	Exelixis proffered and the Court accepted Dr. Myerson as an expert in the subject of separation and purification methods, crystallization, pharmaceutical formulation, and pharmaceutical manufacturing. Dr. Myerson is a Professor of Chemical Engineering at MIT. Tr. 682:23-684:1, 684:14-685:18, 686:2-7 (Myerson); PTX-773.
John Koleng, Ph.D.	Live	Exelixis proffered and the Court accepted Dr. Koleng as an expert in pharmaceutical formulation. Dr. Koleng is the Vice President of Product Development & Manufacturing at TFF Pharmaceuticals, Inc. and an Adjunct Professor at the University of Texas in Austin. Tr. 70:2-21, 71:7-16; Tr. 72:16-19 (Koleng); PTX-777.
Bernhardt Trout, Ph.D.	Live	Exelixis proffered and the Court accepted Dr. Trout as an expert in pharmaceutical development and manufacturing, including with respect to crystallization of pharmaceutical salts. Dr. Trout is a Professor of Chemical Engineering at MIT. Tr. 840:17-24, 842:17-843:4 (Trout); PTX-774.

Witness	Live or By Deposition	Description
Michael Tate	Live	Exelixis proffered and the Court accepted Mr. Tate as an expert in economic analysis as it pertains to commercial success. Mr. Tate is a VP in the IP practice of the consulting firm Charles River Associates. Tr. 977:19-22, 978:12-16 (Tate); PTX-778.
Daniel George, M.D.	Live	Exelixis proffered and the Court accepted Dr. George as an expert in the treatment of cancer, including renal cell carcinoma. Dr. George is a clinical oncologist and a Professor of Medicine at Duke. Tr. 939:16-21, 941:11-15 (George); PTX-775.
Salvatore Lepore, Ph.D.	Live	MSN proffered and the Court accepted Dr. Lepore as an expert in the field of chemistry. Dr. Lepore is a Professor of Chemistry at Florida Atlantic University. Tr. 258:8-9, 259:4-8 (Lepore); DTX-522.
Maureen Donovan, Ph.D.	Live	MSN proffered and the Court accepted Dr. Donovan as an expert in in the field of pharmaceutics, including solid dose drug formulation. Dr. Donovan is a Professor at the University of Iowa. Tr. 184:23-24, Tr. 186:3-7 (Donovan); DTX-505.
Jonathan Steed, Ph.D.	Live	MSN proffered and the Court accepted Dr. Steed as an expert in the formation, characterization, and use of pharmaceutical salts. Dr. Steed is a Professor of Chemistry at Durham University. Tr. 424:1-4, 425:22-426:1 (Steed); DTX-558.
Anthony Mega, M.D.	Live	MSN proffered and the Court accepted Dr. Mega as an expert in the field of medical oncology. Dr. Mega is an oncologist and Associate Professor of Medicine at Brown University. Tr. 990:18-25, Tr. 991:11-15 (Mega); DTX-536.
DeForest McDuff, Ph.D.	Live	MSN proffered and the Court accepted Dr. McDuff as an expert in the field of economics and commercial success. Dr. McDuff works at Insight Economics and is a Teaching Professor at UNC, Chapel Hill. Tr. 1013:6-9, 1013:17-21 (McDuff); DTX-530.

These Proposed Findings of Fact supplement Exelixis' Opening Proposed Findings of Fact on Infringement, D.I. 168.

I. Proposed Factual Findings Relevant to the Crystalline Malate Salt Patents

A. Level of Ordinary Skill in the Art

1. A skilled artisan for the Crystalline Malate Salt Patents would have had at least a bachelor's degree in chemistry, chemical engineering, pharmaceutical sciences, or a related discipline, along with several years of experience working in pharmaceutical development and/or solid-state chemistry and would have also been part of a team which would have included synthetic organic chemists and process chemists, formulation scientists and analytical scientists, and clinicians. Tr. 844:9-24 (Trout). MSN's expert Dr. Steed relied on a similar definition, and both experts testified that their opinions would not change based on the definition applied. Tr. 430:2-17 (Steed); Tr. 845:3-8 (Trout).

B. Invention of the Crystalline Malate Salt Patents

2. An active pharmaceutical ingredient is the compound in a drug product that provides the therapeutic activity. Tr. 800:16-20 (Koleng). Properties of a compound such as low stability, purity, or solubility may be modulated with formulation techniques such as salt formation, nanomilling, micronization, and the preparation of solid amorphous dispersions. Tr. Tr. 510:6-12 (Steed); 590:2-8 (Shah); Tr. 800:21-801:9 (Koleng); Tr. 879:7-18 (Trout).

3. Crystalline cabozantinib (L)-malate is formed by reacting cabozantinib free base and (L)-malic acid. JTX-1 at 18:61-64, 22:22-40; Tr. 589:6-8, 597:7-9 (Shah); Tr. 943:18-22 (George); PTX-1 at 1, 27; PTX-4 at 1, 13.

4. A salt may form when a compound, generally dissolved in a solvent, reacts with an acid or a base. Tr. 431:5-7 (Steed); Tr. 801:23-25, 804:11-22 (Koleng). At the priority date of the Crystalline Malate Salt Patents, a skilled artisan seeking to make a salt for a particular compound

could not have predicted whether such a reaction would form any specific salt or whether any resulting salt would have properties suitable for pharmaceutical development. Tr. 528:10-18, 532:8-12, 532:18-533:2 (Steed); Tr. 799:17-23,828:3-9 (Koleng). Salt formation and salt properties are unpredictable and depend on the compound, the acids used, and the reaction conditions (e.g., the solvent, temperature, agitation rate, and experimental procedure), and do not always improve a compound's properties. Tr. 802:1-803:8, 804:11-22, 806:20-807:14, 807:22-808:16, 825:13-16 (Koleng); PDX-5.6. "Salt screens" were often limited to the most commonly used acids and even so the results were unpredictable. Tr. 802:1-15, 828:3-12 (Koleng); Tr. 529:3-531:1 (Steed); Tr. 883:14-23 (Trout); PTX-333 at 1; PTX-327 at 1.

5. A salt may be crystalline or amorphous. Tr. 846:4-19 (Trout); Tr. 531:6-7 (Steed). The plain and ordinary meaning of "crystalline" describes a material in which the structural units are repeated regularly in three dimensions, while amorphous material does not contain long-range order. Tr. 534:18-535:19, 537:17-19 (Steed); Tr. 846:4-19, 853:7-23 (Trout). Crystalline material is usually more stable than amorphous material, while amorphous material usually has a more favorable dissolution profile than crystalline material. Tr. 441:13-18, 442:16-21 (Steed); Tr. 893:19-894:1 (Trout). Crystalline and amorphous material can be distinguished using analytical techniques such as microscopy, X-ray powder diffraction, and differential scanning calorimetry. Tr. 542:10-543:2 (Steed); Tr. 846:4-19 (Trout). The FDA has approved both crystalline and amorphous drugs. Tr. 441:13-23 (Steed).

6. Exelixis determined that cabozantinib free base was unstable and not suitable for development. Tr. 589:24-590:8 (Shah). Exelixis explored formulation approaches, including preparation of cabozantinib salts. Tr. 577:18-578:3 (Lamb); Tr. 591:2-11 (Shah).

7. Exelixis directed a contractor, Pharmorphix, to conduct a salt screen. Tr. 591:12 23 (Shah); PTX-87 at 1. Pharmorphix evaluated twenty-seven solvents and determined two were suitable. Tr. 804:11-806:8 (Koleng); PTX-87 at 6. Pharmorphix then experimented with twenty-two acids and recommended five salts, including the (L)-malate salt, for further evaluation. PTX-87 at 3; Tr. 591:24-592:7, 622:15-21 (Shah). For the five salts, Exelixis conducted bioavailability testing in animals and determined photostability and solubility in biorelevant media. Tr. 580:25-583:12 (Lamb); Tr. 591:24-592:14 (Shah); PTX-94 at 21, 155-156, 162-168, 173, 183-185.

8. Exelixis selected the crystalline (L)-malate salt because of its high bioavailability and excellent solid-state properties. Tr. 592:15-593:2, 595:4-16 (Shah); Tr. 524:19-525:1 (Steed); Tr. 851:6-12 (Trout); JTX-1 at 7:54-8:24. Although the (L)-malate salt did not have the best solubility, cabozantinib's high permeability, long half-life, and active metabolite provided sufficient bioavailability. Tr. 593:3-594:5, 595:4-16 (Shah); Tr. 851:13-20 (Trout); JTX-1 at 7:57 (describing cabozantinib free base as having "very low solubility").

9. The Crystalline Malate Salt Patents claim priority to U.S. Provisional Patent Application No. 61/145,421, filed on January 16, 2009. Tr. 428:8-10, 453:19-454:2 (Steed); Tr. 844:7-8, 855:1-16 (Trout). '439 patent claim 4 recites crystalline cabozantinib (L)-malate. JTX-1 at 32:22-24, 32:28-36. '440 patent claim 3 recites a pharmaceutical composition comprising cabozantinib (L)-malate or (D)-malate. JTX-2 at 32:16-21. '015 patent claim 2 recites a method for treating kidney cancer with crystalline cabozantinib malate. JTX-3 at 32:11-16.

10. The specification includes the chemical formula for crystalline cabozantinib malate. It also includes preparation methods and characterization data for both crystalline and amorphous cabozantinib malate, including X-ray powder diffraction, nuclear magnetic resonance, thermogravimetric analysis, and differential scanning calorimetry data. JTX-1 at 2, 1:24-53, 3:41-

46, 3:50-4:38, 7:32-36, 7:54-8:40, 12:1-28, 14:6-15:12, 17:10-18:57, 18:59-23:60, 24:34-47; 24:49-32:19; Tr. 539:16-25 (Steed); Tr. 858:10-23 (Trout).

11. The specification demonstrates that crystalline cabozantinib (L)-malate salt had the most favorable pharmaceutical properties of the salts tested. JTX-1 at 7:32-45, 7:54-8:24. As "[a]nother aspect" of the invention, the specification describes the crystalline forms N-1 and N-2, which are similar but not bioequivalent. JTX-1 at 8:26-28, 18:59-23:60, 24:49-32:19; Tr. 852:8-16, 860:7-12 (Trout); DTX-20 at 1-2.

C. The Crystalline Malate Salt Patents Adequately Describe Crystalline Cabozantinib Malate

1. "Crystalline" Cabozantinib Malate

12. The claims use "crystalline" as an adjective to describe the malate salt. Tr. 534:9-17 (Steed). Solid matter can exist as amorphous or crystalline material. Tr. 846:4-19 (Trout). In the claims, "crystalline" describes a material in which the structural units are repeated regularly in three dimensions. Tr. 534:18-535:19, 537:17-19 (Steed); Tr. 846:4-19, 853:7-23 (Trout). Amorphous material is not crystalline. Tr. 535:16-19 (Steed); Tr. 846:4-19, 853:7-15 (Trout). The term crystalline differentiates materials with long-range order from amorphous materials. Tr. 535:16-19 (Steed); Tr. 846:4-19, 853:7-15 (Trout).

13. The asserted claims do not use the term "form." Tr. 854:22-25, 855:20-856:1 (Trout). The '776 and '549 patents, which are in the same family as the Crystalline Malate Salt Patents, use the term "form" in the claims, and have claims directed to particular crystalline forms, N-1 and N-2. Tr. 453:21-454:11 (Steed); Tr. 855:10-19 (Trout); JTX-9 at 46-47; JTX-10 at 47.

14. The specification separately describes crystalline cabozantinib and crystalline forms of cabozantinib. *Compare* JTX-1 at 7:32-36 (differentiating crystalline and amorphous cabozantinib malate), *and id.* at 7:54-8:24 (Table 1 referring to the cabozantinib (L)-malate salt as

"[c]rystalline" and other salts as "[a]morphous"), *with id.* at 8:26-28 ("Another aspect of this disclosure relates to crystalline forms of Compound (I), which include the N-1 and/or the N-2 crystalline form of Compound (I)"), *and id.* at 8:29-30 (each "form of Compound (I) is a separate aspect of this disclosure."); Tr. 851:21-853:2 (Trout). A skilled artisan could determine whether a material was crystalline without identifying the polymorphic form. Tr. 542:10-25, 543:12-14 (Steed); Tr. 846:4-19, 856:6-857:19 (Trout).

2. The Specification Describes Common Structural Features

15. The specification discloses structural features shared by all crystalline cabozantinib malate, including chemical name, formula, and structure. JTX-1 at Abstract, 1:26-39, 2:58-3:12, 5:25-6:67; Tr. 866:10-867:3 (Trout). A skilled artisan would have been able to discern crystalline cabozantinib malate from (i) amorphous cabozantinib malate, (ii) other crystalline cabozantinib salts, and (iii) malate salts of other pharmaceutical compounds. JTX-1 at 5:25-6:42, 18:36-39, Figs. 1-27; Tr. 542:10-25 (Steed); Tr. 846:4-19, 856:6-24, 866:10-867:3 (Trout). A skilled artisan would have understood that all crystalline cabozantinib malate had ordered long-range structure identifiable by analytical techniques described in the specification and known in the art. JTX-1 at Figs. 1-27, 18:36-39; Tr. 542:10-543:2 (Steed); Tr. 856:11-14, 866:10-867:3 (Trout).

3. Forms N-1 and N-2 Are Representative

16. The genus of cabozantinib malate forms is not infinite. The maximum number of polymorphic forms identified for any compound in history is fourteen. Tr. 547:2-5 (Steed). In the more than twenty years that cabozantinib has been studied by Exelixis, MSN, Mylan, and Cipla, only three distinct crystalline forms of cabozantinib (L)-malate have been identified by reliable data: Exelixis' Forms N-1 and N-2 and MSN's Form S. 865:19-866:1, 912:7-15 (Trout). Other crystalline forms reported—including the eight MSN identified—are either not crystalline or reflect combinations of other forms. Tr. 865:19-866:1 (Trout).

17. Mylan's Form M_1 is amorphous, not crystalline, as shown by the characteristic broad swale. PTX-256 at 2 (Fig. 1), 5:34-65; Tr. 864:24-866:1 (Trout); DTX-222 at 28. An overlay of MSN's Form M with an Exelixis cabozantinib free base form (PTX-783) demonstrates that MSN's Form M is the free base and not an (L)-malate salt. Tr. 861:23-863:4 (Trout). Other putative reported forms relied on by MSN contain multiple peaks overlapping with Forms N-1, N-2, and S, and cannot be identified as distinct crystalline forms. Tr. 550:18-21 (Steed); Tr. 865:19-866:1 (Trout). Even accepting Dr. Steed's flawed analysis, there are only eight forms beyond Forms N-1, N-2, and S.

18. Forms N-1 and N-2 are both suitable for use in pharmaceutical compositions. Tr. 859:23-860:16 (Trout); DTX-20 at 1-2.

19. There are no reported solvated or hydrated forms of crystalline cabozantinib malate. Tr. 866:2-7 (Trout). Solvates and hydrates would have a different molecular formula than the non-solvated or anhydrous form. Tr. 540:1-4 (Steed).

20. The Mylan patent filing does not refer to Form M_1 as a "solvate" and does not provide a chemical formula consistent with being a solvate. DTX-222 at 1-2, 7-8, 18 (referring to polymorphs, not solvates); 18-19 (Examples 1-3 do not refer to solvates); *id.* at 23-26 (claiming crystalline polymorphic forms).

21. MSN represented to FDA that Form S, the active ingredient in MSN's ANDA Product, has the same chemical name, molecular formula, molecular weight, and chemical structure as the active ingredient in Cabometyx®; nowhere (including in its patent filings) does MSN identify Form S as a solvate or hydrate. *Compare* DTX-215 at 16 *and* PTX-698 at 12, *with* PTX-1 at 27; Tr. 866:2-7 (Trout); DTX-333 at 1, 11, 14:27-45, 26:65-29:6.

D. The Asserted Claims are Patentably Distinct from Claim 5 of the '473 Patent

1. Claim 5 of the '473 Patent

22. Claim 5 of the '473 patent issued on August 25, 2009 and is directed to cabozantinib or a pharmaceutically acceptable salt thereof. DTX-13 at 1, 412:34-51. Claim 5 does not require a salt. Tr. 490:25-491:15 (Steed); 869:22-24 (Trout). Nor does it recite any particular salt. Tr. 490:25-491:15 (Steed); 870:2-10 (Trout). Claim 5 also does not recite a pharmaceutical composition of cabozantinib or a method of treating kidney cancer with cabozantinib, as recited by claim 3 of the '440 patent and claim 2 of the '015 patent, respectively. Tr. 491:16-21 (Steed).

23. The specification of the '473 patent, which is the same as the specification of the '928 publication, exemplifies more than 400 novel tyrosine kinase inhibitors. DTX-13 at 20:66-174:33 (Table 1), 194:48-245:18 (Table 2); Tr. 495:22-496:2 (Steed). None of those compounds is a malate salt, and malic acid is not mentioned in the '473 patent. Tr. 494:8-10, 495:2-7, 495:22-496:8 (Steed). The specification's definition of "pharmaceutically acceptable acid addition salt" lists twenty-four acids, none of which is malic acid. Tr. 493:20-494:10 (Steed); DTX-13 at 270:15-25. While some of the 88 synthetic examples in the specification disclose preparation of a salt, none prepares a malate salt. Tr. 495:2-7 (Steed). The synthetic example describing how to prepare cabozantinib—Example 48—does not include a salt formation step or otherwise identify any need to prepare a salt. Tr. 495:8-21, 498:22-24 (Steed); DTX-13 at 324:47-325:52.

2. No Motivation to Pursue a Salt, Let Alone a Crystalline Malate Salt

24. About half of FDA-approved drug products are developed as non-salts. Tr. 510:9-12 (Steed). A skilled artisan would have considered making a salt only if there were problems with the free base. Tr. 500:19-501:6 (Steed); DTX-167 at 30-32. There were no reported problems with cabozantinib free base in the prior art. Tr. 874:12-875:1 (Trout); DTX-13. As of the priority date, cabozantinib's oral bioavailability, gastrointestinal absorption, solubility, permeability, or in vivo potency were not known, let alone associated with problems. Tr. 501:7-25 (Steed); Tr. 875:2-10, 878:6-9, 878:24-879:4 (Trout).

25. In selecting a salt, a skilled artisan would have considered a compound's potency, permeability, and bioavailability in addition to its solubility. Tr. 824:19-825:7 (Koleng); 877:7-14 (Trout). If a skilled artisan had tested cabozantinib, they would have learned that it was highly permeable, and its bioavailability was not driven by solubility. Tr. 877:19-23 (Trout); Tr. 593:3-594:5, 595:4-16 (Shah).

26. As of 2009, a skilled artisan would have been aware of at least 113 potential acids for salt formation. Tr. 500:4-12 (Steed); Tr. 823:9-12 (Koleng); Tr. 873:17-24 (Trout).

27. A skilled artisan would have known that preparing pharmaceutical salts was complex, unpredictable, and driven by many considerations, including the properties of the compound and acids, and therefore salt screens were not always successful. Tr. 799:17-23, 801:23-803:8, 807:22-808:16; 809:4-810:5, (Koleng). The pK_a and solubility of cabozantinib were not described in the prior art, and the conditions needed for salt formation were unknown. Tr. 804:11-22, 809:4-810:5 (Koleng). Experimentally determining a compound's pK_a and conducting a solvent screen would have taken "quite a bit" of work. Tr. 838:2-839:9 (Koleng). A skilled artisan would have recognized cabozantinib as a weakly basic compound based on the quinoline ring in its structure. Tr. 809:24-810:5 (Koleng); PTX-373 at 6, 13 (reporting quinoline as having a pK_a of 4.9). Stronger acids would have been favored for use with a weak base such as cabozantinib to create a larger pK_a difference, increasing the potential for salt formation. Tr. 507:11-19, 523:1-6 (Steed); Tr. 808:19-809:3 (Koleng). The pK_a difference between malic acid (pK_a ~3.4) and quinoline (pK_a 4.9) is 1.5. Tr. 810:12-14 (Koleng); PTX-373 at 7 (reporting malic acid as having a pK_a of 3.4).

28. Under the "Rule of Two" discussed by Dr. Steed—one of many potential guidelines for acid selection—the "acid should be at least two pH units lower than the pK_a of the compound."

Tr. 437:3-9 (Steed). Based on this 1.5 pK_a difference, a skilled artisan would not have selected malic acid to form a salt with a quinoline-containing compound. Tr. 437:3-9 (Steed); Tr. 811:10-812:17 (Koleng); Tr. 880:12-17 (Trout). Satisfying the Rule of Two does not guarantee that a salt will form. Tr. 812:23-813:3 (Koleng).

29. The hierarchical approach to salt formation described in the prior art begins with the strongest and most widely used acids. Tr. 507:8-19 (Steed); Tr. 813:4-12, 814:1-8, 814:17-25 (Koleng); DTX-167 at 30-31. Under the hierarchical approach, a skilled artisan would have started with hydrogen chloride, the most commonly used counterion in FDA-approved salts and one of the strongest acids. Tr. 507:8-19, 508:3-21 (Steed); Tr. 814:17-25 (Koleng); DTX-167 at 30-31. A skilled artisan would then have considered other strong mineral acids (i.e., inorganic acids, including hydrogen bromide, and sulfuric, nitric, and phosphoric acid). Tr. 815:1-20 (Koleng); DTX-167 at 30-31. Only if stronger inorganic acids were unsuitable would a skilled artisan turn to organic acids. Tr. 816:18-818:1 (Koleng); DTX-167 at 30-31.

30. Organic acids are generally disfavored for salt formation because they are weaker acids, include multiple functional groups that can cause complications, and have higher molecular weights, adding unfavorable bulk. Tr. 817:19-818:1 (Koleng). If organic acids were considered, stronger organic acids, such as maleic and methanesulfonic acid, would have been favored over weak organic acids, such as malic acid. Tr. 816:23-817:13 (Koleng).

31. Less than 0.5% of FDA-approved salts are malate salts. Tr. 821:8-13, 822:10-19 (Koleng); DTX-167 at 4-5; PTX-782; DTX-177 at 3. Neither Dr. Steed nor Dr. Koleng has ever made a malate salt, and Dr. Koleng, who has conducted ten salt screens with many different counterions, has never used malic acid. Tr. 488:21-489:2 (Steed); Tr. 799:2-10, 823:2-8 (Koleng).

32. Malic acid is also "doubly ionizable," which increases the complexity of its use,

and can result in "pseudodimerism," where two molecules of malic acid react to form an impurity. Tr. 506:22-507:7 (Steed); Tr. 810:12-14, 817:19-818:1 (Koleng); 881:20-882:8 (Trout); PTX-333 at 12 (malic acid is a "complicated" choice).

33. If Dr. Steed's assumed pK_a of cabozantinib (5.8-5.9) were applied, cabozantinib and malic acid have a ~2.5 pK_a-unit difference. Tr. 518:24-519:24 (Steed). To provide the strongest chances of forming a salt, it was "widely accepted that there should be a minimum difference of about 3 units between the pK_a value[s] … especially when the drug substance is a particularly weak acid." PTX-322 at 1-2; *see also* Tr. 520:21-523:14 (Steed); Tr. 880:18-881:17 (Trout); PTX-610 at 171-173. The ~2.5-pK_a unit difference between malic acid and cabozantinib does not satisfy the Rule of Three. Tr. 518:24-519:10 (Steed).

34. GRAS designation would not have been a consideration for the selection of acids to use in a salt screen. Tr. 818:13-819:5 (Koleng). A substance's GRAS designation relates to its use alone in food additives, not combined with another molecule as in pharmaceutical salts. Tr. 818:13-819:5 (Koleng). Using only GRAS acids would have resulted in the exclusion of commonly used acids. Tr. 818:20-819:5 (Koleng); *compare* DTX-177 at 3 (showing frequency of salt), *with* PTX-610 at 338-339 (many commonly used acids, such as hydrobromic, maleic, and methanesulfonic acid, are not GRAS-designated).

35. The Bighley reference discusses potential toxicity of injectable products, not oral drugs, and would have been irrelevant to the selection of a potential counterion for use in an oral dosage form. Tr. 816:2-17 (Koleng); DTX-167 at 36.

36. The prior art does not describe a "structural compatibility" theory. Tr. 882:12-22 (Trout). Even if the bonding pattern proposed by MSN did occur and had been reported in the prior art, it would apply to nearly all organic acids (which nearly universally contain carboxylic

acid groups) and would have excluded common inorganic acids. Tr. 883:1-10 (Trout).

37. A skilled artisan would not have been motivated to make a cabozantinib malate salt by the fact that sunitinib, an FDA-approved tyrosine kinase inhibitor, was developed as sunitinib malate. Tr. 823:20-824:18 (Koleng). Sunitinib and cabozantinib have different chemical structures, and sunitinib is a much stronger base than cabozantinib. Tr. 823:20-824:18 (Koleng).

38. A skilled artisan could have considered the twenty-four acids listed in the '928 publication—a number beyond the typical salt screen—for a cabozantinib salt screen. Tr. 802:10-15 (Koleng); Tr. 872:5-24 (Trout). If a skilled artisan started with those disclosed acids (e.g., hydrochloric, pyruvic, methanesulfonic, or ethanesulfonic acid), they may have formed a salt with suitable properties and may have not conducted additional experiments. Tr. 524:19-525:1, 526:1-527:15 (Steed); PTX-265 at 97 (¶ [0501]); JTX-1 at 8:11-24.

3. No Reasonable Expectation of Success

39. Many variables (e.g., the compound, solvent, acid, stoichiometry, and reaction temperature) can influence the results of a salt screen—i.e., whether a salt forms, can be isolated, and has acceptable properties. Tr. 528:21-529:9 (Steed); Tr. 591:17-23 (Shah); Tr. 799:11-23, 802:1-9, 807:22-808:16, 809:4-810:5 (Koleng); PTX-333 at 1. The solvent used in a salt-formation experiment is a significant and unpredictable element; a skilled artisan would not have had a reasonable expectation as to what solvents would have been suitable without testing them. Tr. 804:11-22, 806:1-16, 838:25-839:9 (Koleng) (solvent screening can take weeks and involve 50-75 solvents). A skilled artisan would have needed to determine the experimental conditions for a salt screen (e.g., reaction temperature, duration, agitation rate, and stepwise procedure). Tr. 806:20-807:8 (Koleng). These conditions would have directly impacted salt formation and a skilled artisan would not have had an expectation as to what conditions would work without performing the experiments. Tr. 807:3-808:16 (Koleng).

40. A skilled artisan would have known there was no way to predict whether a crystalline salt will form. Tr. 807:15-808:16, 828:3-12 (Koleng); Tr. 884:1-19 (Trout). Knowledge of the pK_a difference between the free base and the acid "enable[s] ***potential*** salt forming agents … to be selected," but is not predictive of crystalline salt formation. PTX-322 at 1 (emphasis added); Tr. 803:21-25, 812:23-813:3 (Koleng); 884:20-885:8 (Trout); DTX-243 at 4 (two of six acids that satisfied the Rule of Two only formed "oily," non-crystalline material).

41. A skilled artisan would not have been able to predict how salt formation would impact a compound's properties. Tr. 885:11-886:1 (Trout); Tr. 807:22-808:16 (Koleng). The '473 patent did not provide any direction as to which, if any, cabozantinib salt would have suitable properties for development. Tr. 887:20-888:7 (Trout); Tr. 532:18-533:2 (Steed). Salt screens were often unsuccessful or resulted in salt forms that had less suitable properties than the free base. Tr. 807:22-808:16 (Koleng) (describing an experience where the free base exhibited better properties than any salt formed in the salt screen).

4. Objective Indicia Confirm MSN Cannot Establish Obviousness[1]

42. The active ingredient in Cabometyx® and Cometriq® is crystalline cabozantinib (L)-malate. FOF ¶ 3. The crystalline cabozantinib (L)-malate salt could be manufactured and developed in a stable, safe, and effective formulation. Tr. 894:22-895:2 (Trout).

43. It was unexpected and surprising that crystalline cabozantinib malate exhibited (1) the best overall properties among all the salts Exelixis evaluated (Tr. 889:1-10 (Trout)); (2) faster dissolution compared to amorphous cabozantinib malate (Tr. 889:11-16, 891:1-9 (Trout); 638:19-639:7 (Shah), PTX-225 at 5-8)[2]; and (3) such a fast dissolution profile (i.e., fully dissolved

[1] The commercial success, long-felt need, and blocking patent analysis below is incorporated by reference herein. *See* § III.D.

[2] Amorphous solids were generally understood to have a faster dissolution rate than corresponding crystalline solids. Tr. 893:19-894:1 (Trout); PTX-421 at 28-29.

within 15 minutes) in light of its low water solubility (Tr. 890:13-891:9 (Trout)).[3]

II. Proposed Factual Findings Relevant to the '349 Patent

A. Invention of the '349 Patent

44. As Exelixis proceeded to develop a pharmaceutical product, it initially used Process A, a method developed by the company's medicinal chemists to synthesize small quantities of cabozantinib (L)-malate API. Tr. 599:14-600:7, 602:1-9 (Shah); Tr. 568:2-569:25 (Wilson); Tr. 692:23-693:2 (Myerson). Process A included the initial "A-1 Process" and the modified "A-2 Process." Tr. 569:3-7 (Wilson); Tr. 602:1-9 (Shah); Tr. 672:11-19 (Myerson).

45. The A-2 Process consisted of five synthetic steps. DTX-291 ¶ [0099]; Tr. 267:13-268:6 (Lepore); Tr 371:10-13 (Donovan); Tr. 707:24-708:17 (Myerson); Tr. 665:5-9, 667:14-668:1 (MacMillan). In Step 1, starting material known as 1-1—i.e., the compound 6,7-dimethoxy-quinoline-4-ol—is reacted with acetonitrile and phosphorus oxychloride to form the 1-2 intermediate, which is crystallized out. PTX-35 at 6, Fig. 8; Tr. 664:7-15, 665:10-19, 666:18-667:4 (MacMillan). In Step 2, the 1-2 intermediate is reacted with 4-nitrophenol in 2,6-lutidine solvent and DMAP base to form the 1-3 intermediate. PTX-35 at 6, Fig. 8; Tr. 667:20-24 (MacMillan). In Step 3, the 1-3 intermediate is reduced to form the 1-4 intermediate. PTX-35 at 6, Fig. 8; Tr. 667:20-24 (MacMillan). In Step 4, the 1-4 intermediate is reacted with an acid chloride compound and purified to form cabozantinib freebase. PTX-35 at 6, Fig. 8; Tr. 667:20-668:1 (MacMillan). In Step 5, cabozantinib (L)-malate is formed by adding cabozantinib free base to malic acid in THF solvent and crystallizing the API out of the solution. PTX-35 at 6, Fig. 8; Tr. 665:5-9, 667:25-668:1 (MacMillan).

46. The A-2 Process (also referred to as the "Brown Process") is disclosed in Example

[3] A skilled artisan would have expected low water solubility to correlate with slow dissolution, yet crystalline cabozantinib malate showed the opposite. Tr. 533:3-6 (Steed); Tr. 891:15-19 (Trout).

1 of Exelixis' 2010 International Patent Application No. WO 2010/083414 to Brown (the "Brown Publication"). Tr. 606:6-15 (Shah); Tr. 709:20-23 (Myerson); Tr. 574:4-575:3 (Wilson); DTX-291 ¶ [0099].

47. Exelixis retained two contract manufacturers—Regis Technologies and Girindus AG—to synthesize cabozantinib (L)-malate using the A-2 Process. PTX-35 at 8-9. Between 2005 and 2007, Regis produced three batches of 7.0 kg, 4.7 kg, and 4.1 kg of the API. PTX-38 at 2, Tbl. 1; PTX-35 at 8-9; Tr. 603:13-16 (Shah); Tr. 716:18-24, 783:7-15 (Myerson). In 2008, Girindus produced one batch of 18.4 kg of the API. PTX-38 at 2, Tbl. 1; PTX-35 at 8-9; Tr. 603:13-16 (Shah); Tr. 783:7-15 (Myerson).

48. The A-2 Process as performed by both Regis and Girindus produced API with significant variation in the levels of many impurities from batch to batch, including the 1-1 impurity. Tr. 600:8-15 (Shah); Tr. 692:15-694:12, 715:17-716:10 (Myerson); PTX-38 at 2, Tbl. 1; PTX-35 at 16, Tbl. 2. The batch produced by Girindus had the highest levels of the 1-1 impurity, ranging as high as 411 or 600 parts per million (ppm) using HPLC/UV testing. PTX-35 at 6-9, 16, Figs. 7, 8, Tbl. 2 (identifying levels of 1-1 impurity in all four batches as 35-411 ppm); PTX-38 at 2, Tbl. 1 (identifying level of 1-1 impurity in Girindus batch as 0.06%, or 600 ppm); Tr. 785:2-10, 789:12-790:3 (Myerson); Tr. 600:8-15, 603:5-23 (Shah). The three batches produced by Regis resulted in levels of the 1-1 impurity ranging from 22 to 44 ppm, depending on the testing method used. DTX-128 at 72; PTX-38 at 2, Tbl. 1; Tr. 715:20-716:10, 718:15-19 (Myerson).

49. The 1-1 impurity was found to form as a degradation product ***during*** the A-2 Process. Tr. 600:8-601:4 (Shah); Tr. 569:16-25 (Wilson); Tr. 671:2-20 (MacMillan). The 1-3 intermediate material in the A-2 Process was found to decompose to form large amounts of the 1-1 impurity. Tr. 693:3-13, 698:16-18 (Myerson); Tr. 600:19-601:4 (Shah); PTX-35 at 9 ("The

competing decomposition pathway of XL184-1-3 to XL184-1-1 under the reaction conditions could not be controlled.").

50. Exelixis discovered the 1-1 impurity was genotoxic by performing *in silico* and Ames testing. Tr. 570:4-17, 571:6-572:1 (Wilson); Tr. 600:8-601:16 (Shah); Tr. 700:5-7 (Myerson); PTX-35 at 9. Genotoxic impurities can damage DNA and cause cancer. Tr. 264:4-10 (Lepore); Tr. 601:17-20, 603:24-604:20, 605:19-606:5 (Shah); Tr. 958:1-960:10 (George). Exelixis was the first to discover the genotoxicity of the 1-1 impurity.

51. Exelixis' Manufacturing Processing Development Report and Batch Analyses submitted to the FDA stated that the A-2 Process resulted in levels of the 1-1 impurity ranging from 35-411 ppm, using HPLC/UV testing (PTX-35 at 16, Tbl. 2; Tr. 716:18-24 (Myerson); Tr. 601:21-603:12 (Shah)), and even reached 600 ppm, depending on the testing method used. PTX-38 at 2, Tbl. 1. Exelixis also reported to the FDA its discoveries that the 1-1 impurity was genotoxic (PTX-38 at 10) and formed as a degradation product (PTX-35 at 7).

52. After discovering that the 1-1 impurity was genotoxic and resulted from degradation during synthesis of the API, Exelixis feared that the 1-1 impurity would further increase when the API was exposed to heat, water, and oxygen during manufacturing. Tr. 604:21-605:6 (Shah). Exelixis thus determined that it was critical to essentially eliminate the impurity from the ultimate drug formulation. Tr. 603:24-606:5, 614:24-615:8, 617:3-14 (Shah); Tr. 575:24-576:24 (Wilson); Tr. 957:22-960:10 (George). To achieve that goal, Exelixis believed that it was "extremely important to ensure that we had the lowest levels possible [of the 1-1 impurity] in the API." Tr. 605:19-24 (Shah).

53. Exelixis scientists significantly modified the A-2 Process. Tr. 603:24-606:5, 605:19-24, 607:4-12, 608:1-10 (Shah). The redesigned process, referred to as the B-2 Process and

exemplified in the '349 patent, took eight years to develop. Tr. 692:23-695:14 (Myerson); Tr. 602:1-606:5, 608:23-25 (Shah); Tr. 575:24-576:24, 568:2-569:25 (Wilson); PTX-35 at 10-13.

54. Exelixis made four significant changes to the A-2 Process to arrive at the B-2 Process. First, Exelixis changed the synthetic route to eliminate formation of the 1-3 intermediate, which had degraded to form the 1-1 impurity in the A-2 Process. Tr. 673:1-674:5 (MacMillan); Tr. 693:3-19, 694:5-24 (Myerson); PTX-35 at 11 (describing elimination of 1-3 step in B-1 Process). Second, Exelixis replaced the 4-***nitro***phenol used in Step 2 of the A-2 (Brown) Process with a 4-***amino***phenol, a compound with significantly different chemical properties. Tr. 673:1-15 (MacMillan); PTX-35 at 6, Figs. 8, 10. Third, Exelixis switched from DMAP, a relatively mild base used in Step 2 of the A-2 (Brown) Process, to pentoxide, an "aggressive, very strong base." Tr. 673:18-21 (MacMillan); PTX-35 at 8, 12, Figs.8, 10. Finally, Exelixis modified the final salt-formation step to use vacuum distillation, which reduced the heat and water required in the reaction, and also changed the solvent to MEK. Tr. 694:13-695:14 (Myerson); PTX-35 at 11-13 (describing modifications to distillation in the B-2 Process to further reduce levels of the 1-1 impurity). As Dr. MacMillan explained, the B-2 Process performs different steps, involves different molecules, and results in different chemistries than the A-2 Process. Tr. 673:1-674:25 (MacMillan).

55. Exelixis reported to the FDA on its redesign of the API manufacturing process. PTX-35. Exelixis told the FDA that the B-2 Process produced cabozantinib (L)-malate API with consistently lower levels of the 1-1 impurity, ranging from 2-12 ppm. PTX-35 at 16, Tbl. 2; Tr. 605:7-18; Tr. 695:7-696:2 (Myerson).

56. Exelixis conducted excipient compatibility studies for several purposes, including to assess the impact of various excipients on formation of the 1-1 impurity. PTX-47 at 18, Tbl. 4;

Tr. 606:23-608:10 (Shah); Tr. 696:15-697:6, 713:3-14, 730:15-20 (Myerson). Exelixis also conducted studies to determine whether the 1-1 impurity formed when cabozantinib (L)-malate API was exposed to higher temperatures or water. Tr. 603:24-605:6, 607:4-12 (Shah); Tr. 713:3-14, 730:15-20 (Myerson). Exelixis' studies demonstrated that the 1-1 impurity could form when the cabozantinib (L)-malate API was exposed to certain excipients or manufacturing conditions, including heat, water, and oxygen. Tr. 606:23-608:10 (Shah).

57. Because the B-2 Process so successfully suppressed the level of the 1-1 impurity in the API, Exelixis was able to produce a formulation that resulted in levels of the 1-1 impurity consistently below 200 ppm using a variety of excipients and standard manufacturing methods. Tr. 603:24-606:5, 615:12-617:25 (Shah); PTX-35 at 16, Tbl. 2. Exelixis uses the B-2 Process to commercially manufacture Cabometyx® and Cometriq®. PTX-35 at 16, Tbl. 2; Tr. 696:3-5 (Myerson); Tr. 614:24-615:8 (Shah). Out of 180 to 190 commercial batches made, which translates to "50 million tablets and millions of capsules," every single batch of Cabometyx® tablets and Cometriq® capsules has met the company's specifications for low levels of the 1-1 impurity. Tr. 615:12-617:25 (Shah).

58. The '349 patent describes and claims Exelixis' invention. The patent expressly teaches that the 1-1 impurity should be minimized to ensure drug safety for patients. JTX-4 at 22:8-27; Tr. 686:24-687:9 (Myerson). It also describes the B-2 Process and exemplifies specific tablet and capsule formulations of cabozantinib (L)-malate. JTX-4 at 3:29-34, 5:9-17, 21:37-22:27; 24:30-30:61; 5:24-7:9 (Tbls. 1, 2, 2A, 3, 4, 5, 6), 31:1-25; Tr. 407:13-18 (Donovan).

59. Asserted claim 3 recites a formulation of cabozantinib (L)-malate that includes a filler, lubricant, disintegrant, and glidant, and is "essentially free" of the 1-1 impurity, where "essentially free" is defined as 200 ppm or less. JTX-4 at 8:15-19, 34:4-51. Claim 3 is expressly

directed to a formulation, and not to the API alone. Tr. 369:22-370:4, 408:4-16 (Donovan).

60. During prosecution of the '349 patent, Exelixis overcame a rejection in view of U.S. Patent Pub. No. 2012/0035212 to Brown (the U.S. counterpart to the Brown Publication). JTX-8 at 759-73; JTX-8A; *infra* ¶ 81.

B. The Prior Art Does Not Identify the 1-1 Impurity or Disclose a Method for Reducing 1-1 in API or Pharmaceutical Compositions

61. A skilled artisan would not have been motivated to minimize levels of the 1-1 impurity in the cabozantinib (L)-malate API or pharmaceutical composition. Tr. 659:19-660:7 (MacMillan); Tr. 707:12-708:2 (Myerson).

62. The prior art, including the Brown Publication, does not identify the 1-1 impurity as a problem. Tr. 415:23-417:24 (Donovan); Tr. 356:5-8, 329:24-330:13 (Lepore) (admitting that Brown Publication does not identify the 1-1 compound as a process impurity or provide amounts of impurities that may arise); Tr. 659:19-25 (MacMillan); Tr. 727:14-728:4 (Myerson). Prior to the '349 patent, the 1-1 impurity had not been identified as being genotoxic. Tr. 356:5-8 (Lepore); Tr. 417:12-14 (Donovan) (admitting that the Brown Publication does not describe 1-1 impurity as genotoxic); Tr. 707:21-23 (Myerson); Tr. 660:4-7 (MacMillan); Tr. 418:12-15 (Donovan) (FDA guidances say nothing about 1-1 impurity); Tr. 727:14-728:4 (Myerson). Although the 1-1 impurity is a quinoline derivative, its quinoline structure would not, without more, have led a skilled artisan to conclude that it was genotoxic. Tr. 356:11-16 (Lepore); Tr. 722:14-724:17, 769:16-24 (Myerson). Many quinoline compounds (including cabozantinib) are not genotoxic. Tr. 356:11-16 (Lepore); Tr. 722:14-724:17, 725:5-726:16, 769:16-24 (Myerson).

63. The prior art does not identify how the 1-1 impurity formed during synthesis and formulation of cabozantinib (L)-malate. Tr. 707:12-708:2 (Myerson) (no prior art cited by MSN's experts identifies 1-1 impurity as process impurity or degradation impurity); Tr. 415:23-416:1

(Donovan) (admitting that prior art does not describe mechanisms of degradation of cabozantinib (L)-malate). Nothing in the prior art taught the role of temperature, water, or acidity in the formation of the 1-1 impurity. Tr. 416:2-15 (Donovan). The prior art did not teach how to reduce the 1-1 impurity in a drug product. Tr. 415:23-417:5 (Donovan).

64. A skilled artisan would not have been motivated to control for the 1-1 impurity in synthesizing cabozantinib (L)-malate simply because 1-1 was a starting material in the Brown Process. Tr. 668:16-669:14 (MacMillan); Tr. 708:23-709:19, 721:12-722:25 (Myerson). As set forth in the Brown Publication, only 2% of the 1-1 starting material remained halfway through the first step of the synthetic process. Tr. 666:4-17, 667:12-668:1 (MacMillan); DTX-291 ¶¶ [0099], [00102]. In addition, the chemical bond in cabozantinib that needs to break in order for the 1-1 impurity to form is highly stable; a skilled artisan would not have expected this bond to break or degrade to form the 1-1 impurity. Tr. 661:1-662:15, 663:8-11 (MacMillan). And, even if it did degrade, the first step of the Brown Process required further purification, and there were four subsequent steps each with their own purification. Tr. 667:10-669:6 (MacMillan). Given these purification steps, a skilled artisan would not have expected the 1-1 impurity to appear in the final product of the A-2 Process. Tr. 661:1-662:15, 663:8-11, 666:18-668:1, 668:16-669:6 (MacMillan); DTX-291 ¶¶ [00102]-[00106], [00111]-[00114].

65. The prior art does not disclose how to formulate cabozantinib (L)-malate essentially free of the 1-1 impurity, or identify any such formulation. Tr. 416:21-23 (Donovan) (admitting that the prior art does not explain how to reduce formation of 1-1 impurity in a drug product); Tr. 418:12-15 (Donovan) (admitting that she had not identified any FDA guidance documents that describe how to control impurities in cabozantinib (L)-malate API); Tr. 421:7-13 (Donovan) (admitting that she had not identified a specific pharmaceutical composition of cabozantinib (L)-

malate that would be obvious over the prior art and essentially free of the 1-1 impurity); Tr. 419:17-420:4 (Donovan) (admitting that Lachman textbook on formulations does not explain how to control for genotoxic impurities in any of its exemplary formulations); Tr. 733:3-14 (Myerson).

66. Dr. Lepore's analysis focused on cabozantinib (L)-malate API; he did not provide opinions on formulation issues. Tr. 314:4-315:4 (Lepore).

67. Dr. Donovan has never worked to control genotoxic impurities in a drug product that was in clinical trials. Tr. 421:21-422:3 (Donovan). Dr. Donovan relied upon Dr. Lepore's opinions about the API in rendering her ultimate opinion regarding obviousness. Tr. 371:17-19, 408:17-409:19 (Donovan).

68. Achieving API essentially free of the 1-1 impurity does not necessitate that a formulation of that API would be similarly pure. Tr. 701:19-702:7, 707:24-708:2, 733:18-734:13, 739:25-740:11 (Myerson). The presence of impurities in the API suggests that those impurities would also be found in the final product. Tr. 412:17-23 (Donovan). Manufacturing exposes an API to heat, humidity, and excipients, which can cause degradation and thereby lead to increased impurity levels. Tr. 414:13-25 (Donovan); Tr. 689:17-690:6 (Myerson).

69. Dr. Donovan did not identify any specific ***formulation*** of cabozantinib (L)-malate allegedly taught by or obvious over the prior art that would necessarily be essentially free of the 1-1 impurity. Tr. 420:21-421:13 (Donovan).

70. Each API has unique properties and reacts to temperature, water, and chemicals in different ways. Tr. 412:6-16, 413:21-414:2 (Donovan). Dr. Donovan did not identify any prior art reference disclosing the physicochemical properties of cabozantinib (L)-malate. Tr. 417:2-5 (Donovan). A skilled artisan would not have had a reasonable expectation of success in creating a pharmaceutical formulation essentially free of the 1-1 impurity based on the prior art. Tr. 733:18-

734:13, 739:25-740:11 (Myerson).

C. Trial Evidence Undermining MSN's Obviousness Theories at Trial

71. The Brown Publication states that "it should be understood that many variations and modifications can be made while remaining within the spirit and scope or the invention. It will be obvious to one of skill in the art that changes and modifications can be practiced within the scope of the appended claims." DTX-291 ¶ [00213]. Example 1 of Brown uses the term "approximately" twenty-seven times when referring to quantities of reagents, temperatures, and times used in the synthetic process. DTX-291 ¶¶ [0063], [00102], [00104], [00106], [00108], [00112], [00114], [00120], [00147], [00162], [00166], [00193], [00194], [00196], [00107], [00199], [00200], [00204]; Tr. 786:2-788:7 (Myerson); Tr. 333:2-8 (Lepore). Exact reproducibility is not attainable in any scientific experiment, even at the level of 99.9% versus 100%. Tr. 333:14-18 (Lepore). That difference of 0.1% equates to 1000 parts per million. Tr. 688:1-6 (Myerson).

72. Exelixis told the FDA that both the Regis and Girindus batches were made using the process disclosed in Brown. PTX-38 at Tbl.1 (Exelixis' IND discloses that the Girindus batch was prepared via the A-2 Process); Tr. 717:22-718:4 (Myerson).

73. There is no evidence that the 1-1 impurity levels in the API produced by Girindus resulted from planned deviations. Tr. 717:3-21, 716:18-717:2, 717:6-718:4 (Myerson). Each of the nine Girindus deviations was made with the purpose of increasing yield and reducing the amount of impurities. Tr. 717:6-10 (Myerson). Most of the deviations in Girindus centered around intermediate steps in the Brown Process which, according to Exelixis' studies, had no role in the formation of the 1-1 impurity. DTX-62 at 14, 18, 21, 25; Tr. 717:17-21 (Myerson).

74. The three batches made by Regis included processing and reagent changes to the Brown Process. PTX-10 at 9 ("The following description of the process is an example of the

current route and scale used in the production of the drug substance…at Regis Technologies, Inc.… ***Some processing and reagent changes were implemented*** for the GMP batch.…" (emphasis added)); Tr. 790:4-21 (Myerson); Tr. 335:19-336:2, 337:22-338:11 (Lepore).

75. The Girindus batch had higher overall purity levels than the Regis batches. Tr. 717:6-21, 789:5-11 (Myerson); PTX-38 at 2, Tbl. 1. The three Regis batches displayed considerable variations in purity. Tr. 795:18-796:4 (Myerson); PTX-38, Tbl. 1 (overall impurities in Regis batches ranging from 0.54-0.87%, with wide disparities in some impurities, including range of 0.07-0.38% for XL-184-1-5A, and range of XL184-1-4 from undetectable to 0.05%).

76. Dr. Lepore did not explain how data from three batches is sufficient to prove that the Brown Process necessarily produces API with low levels of the 1-1 impurity. Tr. 715:20-716:13 (Myerson).

77. In order to eliminate the unacceptably high levels of 1-1 impurity in the API, Exelixis made significant changes to the synthetic process. Tr. 671:10-20, 673:1-674:15 (MacMillan); Tr. 357:20-359:15 (Lepore); Tr. 796:16-20 (Myerson); *supra* ¶¶ 53-55. Exelixis did not control for the 1-1 impurity by simply adding a recrystallization step. Tr. 357:13-15, 359:2-15 (Lepore); Tr. 671:6-20, 675:1-11 (MacMillan).

78. No prior art describes how recrystallization could be used to eliminate the 1-1 impurity. Tr. 307:23-311:3 (Lepore). MSN's experts did not identify any prior art in which recrystallization was used to purify a compound to the less than 200 ppm level of the claimed invention. Tr. 796:16-20 (Myerson).

79. A skilled artisan seeking to reduce the 1-1 impurity to the claimed levels would not have been motivated to use a "recrystallization" process or had a reasonable expectation of success doing so. Tr. 737:5-15, 736:13-737:4, 793:25-794:11 (Myerson); Tr. 675:1-11 (MacMillan).

80. Dr. Myerson has particular expertise in recrystallization. Tr. 684:14-685:2, 735:7-23, 736:23-737:4 (Myerson). Reducing the 1-1 impurity, which has a similar structure to cabozantinib (L)-malate API, to levels below 200 ppm via recrystallization would pose a unique challenge, because impurities structurally similar to the desired API can become embedded in the crystalline lattice, making their elimination especially difficult. Tr. 735:7-23, 736:13-22 (Myerson). Recrystallization could produce additional 1-1 impurity because it is a decomposition product of the API. Tr. 737:7-15 (Myerson). The A-2 Process already included purification steps, so a skilled artisan would not have concluded that adding another purification step in the form of recrystallization would be successful. Tr. 675:1-23 (MacMillan).

D. Objective Indicia Confirm MSN Cannot Establish Obviousness

81. Exelixis' discovery that cabozantinib (L)-malate could be formulated and remain essentially free of the 1-1 impurity over time was surprising and unexpected. Tr. 612:1-11, 642:18-643:23 (Shah). In the Declaration that inventor Dr. Shah submitted to the Patent Office, he wrote "[t]he development of a storage-stable pharmaceutical composition of [cabozantinib (L)-malate] was made difficult because exposure to water, atmospheric moisture, or even residual moisture can cause degradation to form [the 1-1 impurity]." JTX-8A ¶ 12, ¶¶ 18-20, 24; *see* Tr. 610:24-611:16, 642:9-17 (Shah).

82. Exelixis began selling Cabometyx® in 2016. Tr. 982:9-14, 985:11-19 (Tate). From 2016-2022, Cabometyx® generated revenues of $4.9 billion in the U.S. alone. FOF ¶ 3; Tr. 985:8-22 (Tate). Cabometyx® is the market leader for second-line therapy (Tr. 984:13-985:22 (Tate)) as well as therapies capable of use as a monotherapy or combined therapy (Tr. 982:20-983:9 (Tate)), and it has a 39% market share of the tyrosine kinase inhibitor market (Tr. 981:14-982:19 (Tate)). Commercial sales of Cometriq® and Cabometyx® have now treated over 55,000 patients in the U.S. alone. Tr. 979:25-980:8 (Tate); PTX-824.

83. Cabometyx® has dramatically extended the lives of patients with kidney cancer, fulling a long-felt, unmet need. Tr. 955:2-10, 949:7-21 (George). Prior to cabozantinib, median survival for patients with renal cell carcinoma was about a year to a little over two years at best, and first-line therapies commonly lost efficacy. Tr. 955:11-20 (George). Compared with the only approved therapy at the time, sunitinib, cabozantinib increased overall survival, delayed disease progression, and improved the objective response. Tr. 949:24-950:18, 955:21-25 (George); PTX-363. Cabometyx® has allowed patients to live longer. Tr. 956:24-957:19 (George).

84. Separately, and parallel to Exelixis' efforts, MSN and other generic companies actively investigated the compound cabozantinib—even after the '473 compound patent issued—and they filed patent applications and received issued patents related to their work. DTX-121.

85. Cabometyx® and Cometriq® both embody the asserted claim of the '349 patent. Tr. 688:12-15 (Myerson); Tr. 422:7-9 (Donovan); Tr. 1026:15-17 (McDuff). A key feature of the invention of the '349 patent is the ability to reliably formulate cabozantinib (L)-malate essentially free of the 1-1 impurity. Tr. 701:19-702:13 (Myerson). The purity and safety achieved by the claimed invention were necessary for the commercial success of Cabometyx® and its satisfaction of long-felt unmet need. Tr. 986:3-21 (Tate); Tr. 688:16-23, 702:8-13 (Myerson); Tr. 957:22-958:13, 959:4-960:10, (George), Tr. 605:7-606:5 (Shah); Tr. 1008:6-22 (Mega).

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January 23, 2024

CERTIFICATE OF SERVICE

I hereby certify that on January 23, 2024, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on January 23, 2024, upon the following in the manner indicated:

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